DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/4/11 has been entered.

Claims and Previous Objections/Rejections Status

2. Claims 1,6,11,12,14 and 21-26 are pending in the application. Claims 6,11,12 and 14 are withdrawn from consideration.

3. The rejection of claims 1 and 21-26 under 35 U.S.C. 103(a) as being unpatentable over Weinstock et al. (WO00/78145A1) in view of Edwards et al. (WO02/067761) is maintained.

4. The rejection of claims 3 and 4 as reciting the limitation "imaging moiety" for having insufficient antecedent basis for this limitation in the claim as claim 2 doesn't include an imaging moiety for R^1 to R^{14} which are independently R was withdrawn in the final rejection mailed 4/16/10 due to the amendment to the claims on 3/8/10.

5. The rejection of claims 1,5-8 and 17-30 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention withdrawn in the final rejection mailed

7/28/10 due to the amendment to the claims on 7/13/10 to include limitations for R^2, R^3, R^7, R^8 and R^{12}.

6. The rejection of claims 1 and 21-26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention was withdrawn in the final rejection mailed 1/3/11 due to the amendment to the claims on 10/28/10 to include R^2, R^8 and R^{12} is ^{123}I or ^{18}F.

Specification

7. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract recites, “said imaging agents” and “said pharmaceutical composition”.

Claim Rejections - 35 USC § 103

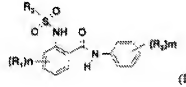
8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weinstock et al. (WO00/78145A1) in view of Edwards et al. (WO02/067761).

10. Weinstock et al. (WO00/78145A1) discloses sulphonamidobenzamide macrophage scavenger receptor antagonists (MSRA) (below) for treating cardiovascular disease including but not limited to atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia, etc. (abstract; p2, lines 26+; p3, lines 8+). R_1 and R_2 may be halo, hydrogen, alkyl, etc.; R_3 may be R_1aryl, etc. wherein R_1 is halo (p3, lines 8-20). The MSRAs may be formulated as pharmaceutical compositions and administered as tablets, liquid preparations, etc. (p11, lines 14+).

11. 

(I)

12. Weinstock et al. does not teach that the at least one halo substituent (R_1 and R_2) is ^{123}I or ^{18}F.

13. Edwards et al. (WO02/067761) discloses detectably labeled macrophage scavenger receptor antagonist (MSRA) complexes for the diagnosis and monitoring of various cardiovascular diseases including but not limited to atherosclerosis, coronary artery disease, renal disease, thrombosis, transient ischemia, etc. (abstract; p37, lines 12-18). The imaging agent disclosed in the present invention is an SR-A antagonist linked to a radioisotope, such as ^{18}F, ^{123}I, etc. (p48, lines 10-20; p49, lines 13-24). The complexes of the disclosure may also include $M\text{-}C_h\text{-}L_n\text{-}(BM)_n$ wherein M is a

radionuclide (i.e. ^{99m}Tc, ^{111}In, ^{113m}In, etc.; C_h is a metal chelator (i.e. a N_4 ligand, N_2S_2 ligand); L_n is a linking group; and BM is a MSRA antagonist (p18-23; p26, lines 19+; p50, lines 6+; see claims). Edwards et al. also teaches of kits comprising the MSRAs of the disclosure (claims 38+).

14. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the MSRA antagonist of Weinstock et al. with a radionuclide for the diagnosis and monitoring of various cardiovascular diseases as Edwards et al. teaches that labeled MSRA complexes are advantageously used for diagnosing and monitoring cardiovascular diseases.

15. At the time of the invention it would have been obvious to one ordinarily skilled in the art to substitute the radioisotope, such as ^{18}F, ^{123}I, etc. of Edward et al. for the halogen substituent of Weinstock et al. to provide SR-A antagonist imaging agents as the results are the predictable advantage of both treating and diagnosing/monitoring cardiovascular diseases.

16. Also, at the time of the invention it would have been obvious to one ordinarily skilled in the art to the formulate the detectably labeled macrophage scavenger receptor antagonist (MSRA) complexes of the combined disclosures of Weinstock et al. and Edwards et al. as a pharmaceutical composition as Weinstock et al. teaches that MSRAs may be formulated as such.

17. The imaging moiety of the combined disclosure encompasses the imaging moiety of the instant claims and is capable of the same functions, such as being

detected externally in a non-invasive manner following administration of said labeled synthetic MSRA antagonist to the mammal body in vivo and has the same properties.

Response to Arguments

18. Applicant's arguments filed 4/4/11 have been fully considered but they are not persuasive.

19. Applicants assert that Weinstock et al. is completely devoid of any test data that would suggest which compound disclosed therein, if any, is promising to modify in order to improve upon its therapeutic activity and obtain a compound with better activity. For example, Weinstock et al. does not disclose any particular compound having a particularly high potency as an MSR antagonist. Then, neither Weinstock et al. nor Edwards et al. provides a reason or motivation to perform the modification (i.e., incorporation of a covalently- bound 123I and ~SF label at the R2, R8 and/or R12 positions of the molecule) that arrives at the claimed compound. The Patent Office therefore appears to have failed to establish the primafacie obviousness of the claimed compounds. See Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007). The Patent Office is respectfully reminded that the compound that appears to be the most promising to modify is not necessarily the compound which is the closest structurally to the claimed compound. Indeed, choosing a compound from the prior art based on the structure of the claimed compounds as a starting point would constitute the use of impermissible hindsight.

20. It is stated in Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007) that prima facie case of obviousness for claimed chemical

compound requires showing of structural similarity between prior art compound and claimed compound, as well as showing that prior art would have suggested making specific molecular changes necessary to achieve claimed invention; this test is consistent with legal principles prohibiting rigid application of "teaching, suggestion, or motivation" test in obviousness inquiry, since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish prima facie obviousness of new compound.

21. Infringement defendants failed to show that prior art suggested making specific molecular modifications to closest prior art compound that are necessary to achieve claimed thiazolidinedione derivatives used as antidiabetic agents, since obtaining claimed compounds from closest prior art compound, identified as "compound b," requires steps of homologating methyl group of compound b, and moving resulting ethyl group to 5-position on pyridyl ring, since evidence supports finding that there was no reasonable expectation in art that adding methyl group to compound b would reduce or eliminate known toxicity of that compound, or that changing positions of substituent on pyridyl ring would result in beneficial changes, since any presumed expectation that compound b and claimed compounds would share similar properties due to their structural similarities is rebutted by evidence that claimed compounds exhibit unexpectedly superior properties over compound b in terms of toxicity, and since record does not support defendants' contention that patentee, during prosecution of prior

patent, stated that making changes to pyridyl region of compound b would lead to "better toxicity" than prior art.

22. The modifications necessary for the thiazolidinedione derivatives involves extensive structural modification of the lead "compound b" whereas the modification to the Weinstock et al. MSR antagonists involves the substitution of a halogen by a finite number of the corresponding radioactive halogen.

23. Weinstock et al. teaches that the MSR antagonists are used to treat cardiovascular disease and therefore, the radioactive modification of the MSR antagonists of Weinstock et al. is advantageous as they can not only treat cardiovascular disease but they can be predictably used as imaging agents to diagnosing/monitoring cardiovascular diseases as Edwards et al. teaches that detectably labeled MSRA complexes are used for the diagnosis and monitoring of various cardiovascular diseases.

24. Applicant asserts that the Patent Office also seems to have overlooked the teachings in Edwards et al. that appear to teach away from the claimed invention. In the Office Action, the Patent Office states that Edwards et al., on page 48, lines 10-20 and page 49, lines 13-24, discloses radioisotopes such as 123I and 18F. But, the Patent Office appears to ignore the fact that all of Edwards' compounds are designed to chelate metals like 6°Cu, 62Cu, 64Cu, 67Cu, 99mTc or 188Re. See, e.g., Edwards et al. item [11] on page 35 and the claims. None of Edward's compounds appear to be designed to carry the radioactive label covalently attached to the compound. Further, Edwards et al. teaches, on the same passage on page 48 that the Patent Office cites,

that "generator-produced radionuclides are considered ideal." Applicants respectfully point out that neither 123I nor 18F are generator-produced isotopes. Rather, they are cyclotron-produced isotopes. Also, the discussion on page 49, line 25 to page 50, line 30, appears to promote 99mTc as an ideal radiolabel. Applicants submit that Edwards et al. appears to be teaching away from the use of 123I and 18F labels in a compound and, instead, appears to be teaching toward the use of chelates, specifically 99mTc chelates. In sum, combining the teachings of Weinstock et al., who focuses on non-radiolabeled compounds, with the teachings of Edwards et al., who focuses on chelates of radioactive isotopes and not on compounds that have the radioactive isotope covalently bound to the compounds, does not lead in an obvious manner to the presently-claimed compounds.

25. The reference of Edwards et al. was not explicitly used to teach of the structure of the SR-A antagonist but does teach that the SR-A antagonist is linked to a radioisotope wherein the radioisotope is useful for gamma scintigraphy (e.g. ^{99m}Tc) or positron emission tomography (e.g. ^{18}F) wherein ^{18}F labeled SR-A antagonists can be prepared and purified by known methods with high specific activity and high radiochemical purity (p47, lines 22+; 48, lines 10-20; p54, lines 7+). The reference of Edwards et al. was used to teach that the SR-A antagonist linked to a radioisotope, such as ^{18}F, ^{123}I, etc. can be used for PET imaging of various cardiovascular diseases.

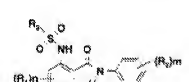
26. Further, all of the embodiments do not have to be exemplified.

27. Applicant asserts that even if Edwards et al. promoted the use of 123I or 18F, he certainly would not suggest or otherwise contemplate making compounds, such as

those claimed, where the 123I or 18F are located at the R2, R8 and/or R12 positions of the molecule. Neither Weinstock et al. nor Edwards et al provides a reason why one of ordinary skill in the art would incorporate the 123I or 18F at the Re, R8 and/or R12 positions.

28. The reference of Edwards et al. was not used to teach of the substitution at the R8 and/or R12 positions of the molecule but was used to teach that the SR-A antagonist linked to a radioisotope, such as ^{18}F, ^{123}I, etc. can be used for PET imaging of various cardiovascular diseases. The SR-A antagonist is linked to a radioisotope wherein the radioisotope is useful for gamma scintigraphy (e.g. ^{99m}Tc) or positron emission tomography (e.g. ^{18}F) wherein ^{18}F labeled SR-A antagonists can be prepared and purified by known methods with high specific activity and high radiochemical purity (p47, lines 22+; 48, lines 10-20; p54, lines 7+).

29. The reference of Weinstock et al. was used to teach of sulphonamidobenzamide macrophage scavenger receptor antagonists for treating cardiovascular disease.



(I) wherein R_1 and R_2 may be halo, hydrogen, alkyl, etc.; R_3 may be R_1aryl, etc. wherein R_1 is halo.

30. The sulphonamidobenzamide macrophage scavenger receptor antagonists have identical core structures to the MSRA antagonists of the instant claims and the modification to the Weinstock et al. MSR antagonists involves the substitution of a

halogen by a finite number of the corresponding radioactive halogen (i.e. ^{18}F) as taught by Edwards et al.

31. Weinstock et al. teaches that the MSR antagonists are used to treat cardiovascular disease and therefore, the radioactive modification of the MSR antagonists of Weinstock et al. is advantageous as they can not only treat cardiovascular disease but they can be predictably used as imaging agents to diagnosing/monitoring cardiovascular diseases as Edwards et al. teaches that detectably labeled MSRA complexes are used for the diagnosis and monitoring of various cardiovascular diseases.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

32. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

33. Claims 1 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what substituents are acceptable for the limitation R^3 as it is not provided.

34. Claims 1 and 21-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation R^2 is recited twice in the instant

claim 1 and therefore, it is unclear as to what substituents are acceptable for the limitation R^2.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 7-4 M, 7-4 T, 6 Th, 7-4 F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa Perreira/

Examiner, Art Unit 1618